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THERAPEUTIC SOLVENT VEHICLE

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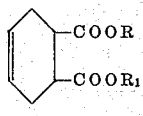
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2 Claims. (Cl. 167—82)

The present invention relates to novel vehicles and therapeutics.

More particularly the present invention relates to combinations of esters of cis-Δ^4-tetrahydrophthalic acid and vegetable oils which have been found to be excellent solvents and vehicles for therapeutic materials both for injection purposes and oral administration.

The esters involved may be characterized by the following general formula:



In the foregoing formula R may be equal to R_1 in the case of symmetrical esters and in that event R and R_1 are straight chain or branch chain alkyl or aralkyl groupings of from six to ten carbons each. For example, both R and R_1 may be hexyl, decyl or octyl.

The unsymmetrical esters of the character described are also within the scope of the present invention and here again R and R_1 may be alkyl or aralkyl radicals and the number of carbon atoms in both R and R_1 may vary between ten and twenty. As typical examples, R may be ethyl and R_1 decyl; R may be butyl and R_1 decyl; R may be hexyl and R_1 decyl and R may be hexyl and R_1 octyl. In the case of the unsymmetrical esters, however, R should contain at least two carbon atoms since the methyl esters have not proven particularly effective for the purposes hereinafter set forth.

The above compounds, in combination with a suitable vegetable oil, have been found to be especially useful solvents for therapeutic agents and have also been effective therapeutics in themselves. The vegetable oils involved are preferably non-drying oils of the type ordinarily used for injection purposes, such as peanut oil, sesame oil or corn oil and in general may be characterized as glycerides or esters of long-chain saturated and unsaturated monocarboxylic acids having from twenty to twelve carbon atoms, inclusive. The vegetable oils involved are, of course, preferably liquid at ordinary temperatures. A great many therapeutic compounds have been found to be highly soluble in the combination of esters and vegetable oil hereinbefore described, and the combination when used for injection purposes has been found to be especially nonirritating and nontoxic. In addition, the vegetable oil and phthalate ester combination above described has been found to enhance the action of certain therapeutics so much as to exhibit a synergistic effect in combination therewith.

An especially desirable composition has been found to be the combination of the dioctyl ester of cis-Δ^4-tetrahydrophthalic acid and a vegetable oil, especially sesame oil, and compounds of the character described in Geschickter and Rubin applications Serial Nos. 118,997 and 118,998, both filed on September 30, 1949, now Patent No. 2,594,418 and Patent No. 2,594,419, have been found to be more effective for the treatment of respiratory diseases than the compounds themselves. For example, pentaquine salicylate, i. e. the salicylic acid salt of 8-(5-isopropylaminoamylamino) - 6 - methoxy quinoline dissolved in the dioctyl ester of cis-Δ^4-tetrahydrophthalic acid and sesame oil, has been found to be especially effective for the treatment of asthma and other respiratory ailments. Further, the combination of the dioctyl ester of cis-Δ^4-tetrahydrophthalic acid and sesame oil has been found to maintain beneficial results in ailments of this same type. The combination of an ester as above described of cis-Δ^4-tetrahydrophthalic acid and a vegetable oil has also been found to be especially effective as a vehicle for dissolving antispasmodic compounds, such as calcium and magnesium salts of alkyl ester of cis-Δ^4-tetrahydrophthalic acid, for example, calcium decyl tetrahydrophthalate, these compounds being disclosed in particular in the application of Reid and Geschickter, Serial No. 753,808, filed June 10, 1947, and now abandoned.

The novel vehicles of the present invention have also been found to be suitable for dissolving antibiotics, such as penicillin and chloromycetin, as well as other therapeutic compounds normally administered by injection. In preparing the vehicles of the present invention the phthalate ester may form from twenty to eighty percent of the vehicle, with the balance eighty to twenty percent by weight being a vegetable oil of the character described. If desired, a portion of the phthalate ester may be replaced by an additional solvent such as benzyl alcohol. In general, however, no more than twenty percent of the vehicle can be benzyl alcohol. However, with the addition of the benzyl alcohol higher concentrations of therapeutic compounds may be achieved.

As an illustration of the use of the present combination as a vehicle a hundred milligrams per cc. solution of calcium decyl tetrahydrophthalate may be prepared in the combination of fifty percent vegetable oil, such as sesame oil, and fifty percent of dioctyl tetrahydrophthalate. A suitable and effective solution of a hundred milligrams per cc. may also be prepared using sixty percent of sesame oil and forty percent of the ester. However, if it is desired to prepare a solution of calcium decyl tetrahydrophthalate having a concentration of two hundred milligrams per cc., a combination best used is twenty percent of benzyl alcohol, forty percent of the dioctyl ester and forty percent of oil. In preparing the solutions of the character just described, the calcium decyl tetrahydrophthalate is first dissolved in the benzyl alcohol, the solution is then added to the ester and finally the oil is added. On the other hand, if no benzyl alcohol is used then the calcium decyl tetrahydrophthalate is first dissolved in the ester and then the vegetable oil added.

The final composition may be utilized for injection purposes, i. e. intramuscular injection or it may be capsulated into suitable capsules and administered orally. The combination has been found to be especially effective as a uterine relaxing agent in cases of dismenorrhea. Similarly, the combination of vegetable oil, such as sesame oil and dioctyl tetrahydrophthalate has been found suitable for preparing relatively high concentration solutions of pentaquine salicylate previously referred to. For example, a mixture of sixty percent vegetable oil, thirty percent of dioctyl Δ^4-tetrahydrophthalate and ten percent of benzyl alcohol will readily dissolve up to thirty milligrams per cc. of pentaquine salicylate. In the absence of the benzyl alcohol forty percent of the phthalate ester and sixty percent of vegetable oil will serve to dissolve up to fifteen milligrams per cc. of pentaquine salicylate.

The following specific examples serve to illustrate but are not intended to limit the present invention:

Example I

Preparation of unsymmetrical esters of cis-Δ^4-tetrahy-

drophthalic acid: The silver salt of decyl cis-Δ^4-tetrahydrophthalic acid was prepared by adding an aqueous silver nitrate solution in excess to a solution of ammonium decyl cis-Δ^4-tetrahydrophthalate which had been made slightly alkaline with ammonium hydroxide. The white silver salt which precipitated was removed by filtration and dried by azeotropic distillation with benzene. To the dry silver salt suspended in the benzene solvent was added an excess of ethyl iodide. The mixture was heated under reflux overnight, filtered from the precipitated silver halide and then fractionally distilled. The ethyl decyl ester of tetrahydrophthalic acid had a boiling point of 148–152° at 0.3 mm. Analysis for carbon showed 71.1% against 71.0% for theory and 10.1% of hydrogen as compared to 10.1% theory.

Similarly prepared were the benzyl decyl ester—boiling point 189–193° at 0.7 mm.; the butyl decyl ester—boiling point 155–160° at 0.3 mm.; the hexyl decyl ester—boiling point 160–163° at 0.3 mm.; and the hexyl octyl ester—boiling point 156–160° at 0.3 mm.

Example II

The preparation of the symmetrical esters of cis-Δ^4-tetrahydrophthalic acid: A mixture of 0.3 mol of tetrahydrophthalic anhydride and the appropriate alcohol (0.8 mol) with 300 mm. of toluene and 0.5 mm. of concentrated sulfuric acid were refluxed for four hours with simultaneous removal of the water formed in the course of the reaction. The toluene and excess alcohol were removed by vacuum distillation and the residual mixture washed with water-sodium carbonate solution, washed free of the alkali with water, dried over magnesium sulphate (anhydrous), filtered and purified by fractionation. By this procedure the following symmetrical esters were prepared:

Diethyl ester from heptyl alcohol and tetrahydrophthalic anhydride—boiling point 163–168°, 0.7 mm. Analysis for carbon 71.8%. Found against 72.1% theory. Analysis for hydrogen found 10.4% against 10.5% theory.

Dioctyl ester from octyl alcohol and tetrahydrophthalic anhydride—boiling point 195–197°, 0.7 mm. Analysis for carbon found 72.8%, theory 73.1%. Analysis for hydrogen found 10.8%, theory 10.7%.

The di-decyl ester from decyl alcohol and tetrahydrophthalic anhydride—boiling point 165–170°, 0.3 mm.

Example III

2000 mg. of pentaquine salicylate were dissolved in 100 cc. of dioctyl cis-Δ^4-tetrahydrophthalate. Thereafter the solution thus formed was added to 100 cc. of sesame oil. The resultant solution was then filled into capsules so that each capsule contained 5 mg. of pentaquine salicylate, ¼ cc. of the phthalate ester and ¼ cc. of sesame oil. A number of patients having asthma were treated with doses varying from one to four of these capsules daily and symptoms were greatly alleviated. The solution was also suitable for intramuscular injection.

We claim:

1. A solvent vehicle for therapeutics comprising from 20 to 80% of the dioctyl ester of cis-Δ^4-tetrahydrophthalic acid and from 20 to 80% of a vegetable oil.

2. A therapeutic composition comprising the salicylic acid salt of 8-(5-isopropylaminoamylamino)-6-methoxy quinoline dissolved in the dioctyl ester of cis-Δ^4-tetrahydrophthalic acid and sesame oil.

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